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THE SEX FACTOR IN DETERMINING THE COURSE OF SYPHILIS*

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THE implications involved in this subject are many, and I hope it will emerge in the course of our deliberations that the factor of the sex of the patient has an intimate and practical bearing not only upon diagnosis and treatment, but upon the future of therapy and upon the public health.

Our object will be best served, I think, if we first of all approach the matter from the purely biological angle, and if we endeavour to obtain a clear conception of what are the essentials of physical maleness and physical femaleness. It is clearly necessary that we must have a very definite idea of what constitutes the basic difference between the two sexes.

There is an average truth which is very striking throughout the whole of the animal kingdom, and it is that of the passivity of the females and the predominant activity of the males.^{1, 2} And, while this is generally true of the relationship of the animal to its surroundings, it is more particularly true of the metabolic processes going on within the body itself. In animals other than the genus homo it is reflected in the gay colourings of the males, and in the quiet and more sedate plumage and coverings of the females. Bright colourings are due, in great part at least, to the presence of pigmented waste products, the result of metabolic activity. The males possess a katabolic diathesis, whereas the female diathesis is anabolic. It will be realised, of course, that a predominantly katabolic diathesis is not necessarily invariably expressed in terms of rapidity of movement.

Without going through a litany of examples, a survey of the animal kingdom shows quite clearly that from the lowest to the highest members the females are essentially

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passive and the males active. In the higher grades of animals this distinction is shown, not in any one great difference of habit, but rather in a multitude of small ways. In the human race, and especially in the more primitive peoples, strenuous and spasmodic bursts of activity—the combat and the chase—are characteristic of the young men; whereas the *rôle* of the woman is rather that of patient, steady effort with but little expenditure of physical energy.

This basic difference between the sexes—between the relatively anabolic female and the more katabolic male—is an expression of a fundamental alternative of variation. There is the same marked contrast between plant and animal, coral and medusa, tortoise and lizard, reptile and bird. The whole thing resolves itself into a contrast between a constructive or conservative physiological habit and one which expresses itself in expenditure and restlessness.

So great is this essential difference between the male and the female, that even in the same species the physical gulf dividing the sexes is wider than that between a particular sex of one species and the same sex of another species. The difference between the lion and the lioness is incomparably greater in a metabolic sense than it is between a bull elephant and a buck rabbit. The essential sex differences are not morphological but metabolical. It is this matter of metabolism—of tissue constitution, of somatic susceptibility and reaction—which is so germane to our subject.

If we hark back to still more rudimentary things, we find the same metabolic state of affairs. At the very beginning of sex differentiation it will be seen that the small active spermatozoön—unable to develop alone—unites in fatigue with the large and quite passive ovum. It has also been shown that the parental environment, particularly in respect of nutrition, is a potent factor in deciding the proportions of male-producing and female-producing cells. Katabolic conditions such as starvation tend to cause male-producing cells; anabolic conditions are prone to cause the opposite result.

There is a mechanism for ensuring the constancy of the sex ratio, and this resides in the chromosomes of the nucleus.³ These chromosomes exist in similar pairs in both sexes; but in the mammalian male one pair is dis-

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similar. Man has one chromosome less than woman ; in other words, he possesses only one member of this pair of special sex-chromosomes. She possesses two. All her ova have one chromosome. Half his spermatozoa possess one, and half possess none. Thus it is when the former kind fertilise an ovum, two chromosomes are present in the fertilised egg and a female individual results. In the other case, where a spermatozoön with no sex-chromosomes fertilises an ovum, only one chromosome is present and so the offspring is a male. The amount of chromatin is an index of anabolic capacity.

We may take it, then, that the male and female are essentially different, even though they happen accidentally to belong to the same species and are morphologically similar ; that this difference lies in the metabolic habit inherent in the tissues ; and that it remains unchanged under varying modifications of environment. It would not, therefore, be very surprising to find that the sexes may react differently to identical stimuli.

Later we shall have to consider the natural variations of sex—the pre-pubertal period, the child-bearing age, the time of pregnancy and lactation, and the post-menopausal era—and we shall see how these variations, all metabolic in essence, operate towards modifying the bodily reaction to syphilis. In the meantime it is, I think, evident, on metabolic and biological grounds alone, that the male and the female are not only different soils, but actually different climates.

In the human race the general distinctions to which I have alluded still remain. The general tendency here is for the male to be smaller, to have a higher body temperature, and to die at an earlier age than the female. All these things indicate a higher katabolism. Absolutely, of course, the woman is the smaller—that is, she weighs about one-third less than the man ; but she is relatively larger since the surface area of her body is greater than a man's in proportion to body-weight. Her metabolism is less intense—anabolic processes predominating.

The relative largeness of the female is not so much an osseous or muscular largeness, but is a " fat largeness." Such a condition is perfectly natural. It is the inevitable expression of the female anabolic habit. The woman possesses more adipose tissue than the man. She has a higher " fat-content." There are, of course, metabolic

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degrees of femaleness among women, just as there are similar variations of maleness among men.

I must emphasize this point of the high fat-content of the female because it is the very crux of my thesis this evening. The connection between fats and lipoids is very close and it will perhaps express my meaning with greater accuracy if I substitute the term "lipoid-content" for "fat-content." In my submission, an understanding of the *rôle* played by lipoids is essential for a proper appreciation of the drama entitled "Syphilis."

Fats are non-nitrogenous substances in which the oxygen of the molecule is not sufficient to combine with the hydrogen. They are the esters of certain fatty acids which may be either saturated or unsaturated compounds. An unsaturated compound is one in which some of the carbon atomic affinities are free. Such compounds readily combine with iodine—through these free affinities—and when they do so the free valencies become saturated. In other words, the iodine saturates the molecule.

In passing, I would call to mind the fibrolytic function of iodides in the therapy of syphilis. There are natural enzymes in the blood whose function is to prevent the formation of fibrous tissue. Gummata, for example, can only be produced when these autolytic ferments have become inactive. In syphilis they become inactivated by the presence of unsaturated lipid radicles with which they combine. The power of the iodides is due to the fact that these unsaturated lipid radicles have a special affinity for iodine which saturates them, and thus leaves the natural ferments free to exercise their autolytic function.

Incidentally one might just mention here the close relationship there is between the secretion of the thyroid with its iodine content and the course of female syphilis. The functional state of the thyroid has a profound effect upon the basal metabolism—hyperthyroidism increasing it by perhaps 75 per cent., and hypothyroidism decreasing it by about 35 per cent. At puberty and pregnancy we know that the thyroid normally hypertrophies and that the metabolic picture is modified at these times. I suggest, then, that it is this lipid metabolism which constitutes the key to which the whole opera of syphilis is set.

Lipoids are like fats in their physical properties and

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solubilities. Chemically, they differ from fats in that some of them contain both nitrogen and phosphorus. Those which are most important are cholesterol and lecithin.

Cholesterol is a mono-hydric unsaturated alcohol. It resembles a fat in so far as it contains neither nitrogen nor phosphorus. It is the most important lipid in the body, is abundant in nerve tissue, and exerts a useful protective influence, forming a shield between the body-cells and toxins. It also prevents the hæmolysis of red corpuscles.

Lecithin is also found in nerve tissue, and it contains phosphorus. It is interesting to note that Russo, the Italian physiologist, found that some ova contain globules of lecithin while others are devoid of it. He showed that the ova with a high lecithin-content produced females, while the others produced males.

Generally speaking, lipoids are constituents of all tissues. In those which are composed of living cells, but which do not serve as storage depôts for fats, the weight percentage of lipoids may be anything from 1 to 10. In tissues which are fat storehouses—such as the subcutaneous fatty tissue, though not the skin itself—there may be as much as 90 per cent. of lipoids. Fat is a lipid-rich tissue, but it is also a low-grade tissue—that is, not highly organised and specialised.

The parasite of syphilis attacks most virulently and most continuously those tissues which are high in the scale of evolution, which are highly organised, which subserve special functions, and which, in addition, are rich in lipoids. There is, moreover, a biochemical similarity between the *treponema pallidum* and the tissues for which it has a predilection, and this lies in the fact that both possess a high lipid-content.

It is true that syphilis attacks low-grade tissue such as the cutaneous and subcutaneous structures, which when destroyed tend to regenerate more or less perfectly, but, even in the absence of treatment, such attack is evanescent and unsustained. That the cutaneous—or rather, the *sub*-cutaneous—tissues are attacked so early and that the assault dies away so quickly are both due to the high lipid-content of these structures.

The propositions I want to put before you at this stage are these :—

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- (1) The *treponema pallidum* directs its main attack upon lipoid-rich tissue, and especially upon that which is both lipoid-rich and highly evolved such as composes the cardiovascular and central nervous systems.
- (2) The higher the lipoid-content of a tissue, the greater is the affinity of the parasite for it in the first instance. Soon, however, some protective process takes place and the attack is beaten off.
- (3) The more highly organised tissues, because they have not so high a lipoid-content as the sub-cutaneous structures, do not attract to themselves the parasites so soon or in such large numbers. For the same reason, they do not elaborate or attract to themselves anti-bodies to the same extent, and so the attack upon them persists.
- (4) The cardiovascular and nervous systems in the male and female are identical, inasmuch as there appears to be no difference in their respective lipoid-contents in the two sexes.
- (5) If, then, other things were equal, syphilis should make no sex-differentiation in attacking these systems.
- (6) We know, however, that in the two sexes there is a most marked modification of the attack upon these systems—that upon the male being very much more severe.
- (7) There must, therefore, be some factor or combination of factors operating upon the virus of syphilis making it more virulent in the male.

My submission is that this sex-modification—the severity of the disease in the male and its mildness in the female—is based upon the metabolic habit and can be expressed in terms of the lipoid-content.

Maleness or femaleness—the degree of lipoid-richness—is intimately related to or dependent upon various endocrine secretions, and chiefly those of the sex-glands. According to the functional activity of these is the lipoid-content raised or lowered.

It is common knowledge that when castration is performed upon boys before the age of puberty, the secondary sexual characters fail to develop. The bodily conformation approximates to that of the female sex. The skin becomes smoother and paler and there is a marked

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increase in the amount of subcutaneous fat. In other words, the lipid-content of the castrated person is increased. The effect of depriving the body of the internal secretion of the testes is to retard katabolism—hence the fattening or general increase of lipid-richness. The internal secretion of the male sex-glands thus has the function of keeping the amount of lipoids stored in the body at a low level.

With respect to the female, we have not the same amount of data. It is only rarely that bilateral ovariectomy is performed before puberty. Nevertheless, there have been many cases of women who, in their early years, have suffered precocious arrest of development of the ovaries. These invariably show a lack of female secondary sexual characters. There is distinct approximation to maleness—that is, a low lipid-content.

Where complete castration is performed on the adult male, about 50 per cent. of cases show no change, while the remainder exhibit various degrees of approximation to femaleness. The facial hair tends to disappear, there is accentuation of the mammary glands, and an increased deposition of adipose tissue chiefly in the hips and thighs. That half the cases show no change is not surprising when we consider that for many years the internal testicular secretion has been going on and as a result the peculiarly male metabolic habit has become thoroughly established. The cases which show a metamorphosis into the female metabolism are those in whom the lipid-content is, naturally, higher than normal.

Bilateral ovariectomy in the adult female produces changes analogous to those of the climacteric period. The main difference is the suddenness with which the change is brought about. In half the cases the woman becomes more obese. In the remainder there is no appreciable metabolic difference or there is an approximation to the male type. Where no change occurs, it is, as in the male, due to the fact that the peculiar sex-metabolic habit has become firmly established. Where an increased lipid-content occurs, as is indicated by obesity, the explanation perhaps is that the internal secretion of the ovaries, aided probably by that of the thyroid, in addition to stimulating lipid storage, also regulates the amount stored. The cessation of the secretion may so upset the balance that in those women who naturally tend towards

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a high lipoid-content, the effect is actually to increase the amount. The women who become markedly thinner and who lose the essentially female characteristics are they who have naturally a low lipoid-content and are of an abnormally katabolic type.

It may be said that a woman only develops her femaleness at puberty and retains it till the menopause. She is, before the former and after the latter, less female than she is between these eras—that is, so far as the basal metabolic processes are concerned. Apart from castration, the man retains his maleness during life, except that he is before puberty less male than at any time after that period.

So much for the biology of the host ; we must now consider, briefly, that of the parasite.

That I regard the parasite of syphilis as a protozoön is indicated by the fact that I use the term "*treponema pallidum*" rather than "*spirochæta*" or "*spironema pallida*." Those who believe it to be a bacterium are influenced chiefly by the views of Dobell, which are based upon morphology. That the parasite is a protozoön is indicated by many things, but more especially by the fact that it behaves as one and does not behave as a bacterium. The type of disease caused by it, its peculiar susceptibility to the action of certain elements belonging to Group V. of the Periodic Table, the peculiar mode of transmission of the disease from parent to offspring, and, finally, the finding of many observers—and most recently by Warthin⁵—of stages of the organism which more than suggest strongly that the spiral form is only one phase of a developmental cycle—all these things point to its protozoal character. Indeed, if we assume that the parasite is a protozoön, then most of the obscurities of syphilis are cleared away. All the facts of the disease square with that assumption. I am aware of none that squares with the idea that it is a bacterium.

I have already said that the parasite is rich in lipoids. It contains, like other protozoa, lecithin-globulin and saturated fatty acids—all of which is very important, as we shall see presently.

Warthin⁵ has well and truly said that "of all the important plagues affecting mankind, no one shows greater differences of reaction and manifestations in the two sexes than does syphilis. In the four centuries in

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which we have had clinical knowledge of this infection, there has occurred one observation after another calling attention to these differences in the clinical picture of syphilis in the two sexes, practically always to the same end, a recognition of its milder quality in the female, of a certain degree of immunity possessed by the latter, and of its tendency to become latent in her during the child-bearing period, but revealing itself in her children."

With that statement there will be no disagreement.

Before puberty, the sex differences of syphilis are slight or non-existent. After puberty, however, say, up to the age of fifty years, syphilis is practically a different disease in the male from what it is in the female. The two sexes react to it as two quite different animals, as, indeed, they are when metabolically considered.

If we momentarily confine our attention to the cardiovascular and central nervous system manifestations of the disease, we shall find it to be generally true that in the female, involvement of these systems is extremely rare during the era from puberty to the climacteric. And when it does occur it is of a trivial degree. It has been noted on several occasions that juvenile general paralysis or tabes occurring in a congenitally syphilitic female child commences to improve with the onset of menstruation, apart altogether from treatment; and conversely, in a similar congenitally neurosyphilitic male child, there occurs at the time of puberty a tendency to progressive deterioration.

At the other end of the scale, the incidence of adult female general paralysis and tabes takes an upward rise after the climacteric has been passed. And this is most noticeable among those women who, after the menopause, become thin—that is, those who lose their lipid-richness. The same is true with respect to the incidence of gummata—after fifty years of age.

Again, pregnancy and lactation cause a distinct modification of the course of syphilis in the female. During that period—and metabolically it is a period of lipid-richness greater than the normal female level—the woman develops a high degree of resistance or immunity to syphilis. Stokes⁶ says that "so influential is pregnancy and lactation in reducing the severity of syphilis in women that one might almost speak of the bearing of children as part of the treatment of the disease."

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The primary lesion is comparatively rarely seen in women ; and this for a variety of reasons. Anatomical differences play a considerable part. In the male there occurs the chancre which is—if we except the rare case of intra-urethral inoculation—an external, superficial, and exceedingly conspicuous lesion. From its site and character it is apt at an early date to attract and to retain the attention of its possessor till it is healed.

The female primary lesion is but rarely on the external genitals, although, paradoxically, that is perhaps the most frequent site upon which it is seen. But even when the inoculation has been upon that area, it does not usually present itself as a typical chancre. It is generally much smaller, less indurated, and is altogether a more evanescent lesion than is found in the male.

A moment's reflection will show, from the very nature of the sexual act, that inoculation upon the female external genitalia is bound to be the *exception* and not the rule. The vagina, the cervix, the cervical canal, and the endometrium, are all more favourably situated for inoculation ; but, of course, these sites are not so easily inspected.

A point with reference to the primary lesion of female syphilis which I suggest is of great importance is this : It is only exceptionally that a man with a penile chancre indulges in sexual intercourse. If not a sense of responsibility, then the pain involved would, as a rule, act as a deterrent. The vast majority of women who acquire sexual syphilis are infected not from a penile lesion, but from spermatic fluid containing *treponemata*—for, as we know, the testes of every male syphilitic in the post-primary stages show the presence of parasites. This accounts for the prevalence of syphilis among the inmates of even the most select and carefully examined houses of prostitution on the Continent, in Egypt, and in India. Such prostitutes are extremely wary in avoiding connection with any man suffering from a venereal disease. Whether their clients realise it or not, the women subject them to what is essentially a careful clinical examination as to the presence or absence of a chancre or urethritis. On the discovery of either of these, intercourse would be refused. And then, even after a presumably healthy connection, the woman douches and adopts various other prophylactic measures. Nevertheless, in spite of

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all that care, it is only a matter of time before these women become infected with either syphilis or gonorrhœa, or both. Although weekly inspections by medical officers are carried out, and in some places this involves the use of a speculum, only rarely is a chancre diagnosed. I do not think that we have any alternative but to conclude that the infection in these cases is by means of the spermatic fluid being deposited upon the columnar-celled mucous membrane of the cervical canal or endometrium, and this, I am convinced, is the usual mode of infection among the female community generally.

Chancre of the cervix is really quite common, and it would be more often recorded were a speculum, rather than the gloved fingers, more frequently used in vaginal examinations. A very high proportion of cervical chancres are wrongly diagnosed as carcinoma. Most of us can quote not a few cases in which a hysterectomy has been done for what was merely the primary lesion of syphilis upon the cervix! Warthin states that every case of primary cervical chancre he has seen was either removed as a cancer or diagnosed in biopsies made on the suspicion of cancer.

The hypertrophied chancre which occurs on the squamous-celled vaginal portion of the cervix, and which presents itself as a cauliflower-like growth, purplish, indurated, and with an eroded or ulcerated surface, is usually labelled "carcinoma." So thoroughly has it been taught and so universally has it been accepted that this is a malignant condition, that when the surgeon meets it clinically he considers a biopsy to be superfluous. The inoculation in such cases has probably been upon an ordinary non-specific cervical erosion.

A solitary erosion upon the cervix, not involving the lips of the os, should always arouse the suspicion of syphilis. By the "finger-tip" method, these are diagnosed merely as "erosions." If such lesions are not dark-grounded, then many chancres will be missed.

Where the inoculation has been upon the columnar-celled tissue of the cervical canal or endometrium, the intensity of the histological reaction is very different from that which takes place elsewhere. This may be shortly expressed by saying that a chancre is not formed. There is present the essential histological picture of a perivascular infiltration of lymphocytes and plasma cells, but

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induration—the typical chancre appearance—is slight or entirely absent. Indeed, the lesion is only identifiable by microscopic examination and is not capable of being diagnosed clinically.

In the secondary and later stages, the sex differences of syphilis are equally well marked. I feel compelled here to make some reference to the statement that women are more prone than men to exhibit constitutional disturbances in the early generalised phases of the disease. Stokes⁷ states that while 63 per cent. of women are constitutionally affected, only 42 per cent. of men are. It must be borne in mind when considering these proportions that they are not really comparable one with the other. The vast majority of males suffering from secondary syphilis present obvious cutaneous and other signs, and the result is that very few cases escape recognition. The reverse is true of women. The majority of female cases are *not* identified. The figures given by Stokes apply therefore to the majority of the males affected, but only to the discovered minority of females. These latter are discovered chiefly because their syphilis is of a more virulent and obvious character than is usually the case in women. Indeed, it is often the presence of constitutional disturbances which arouse the suspicion of syphilis in women, and as a result of that suspicion a more careful clinical examination reveals signs of the disease which would otherwise have been overlooked. The proportions given then, from a majority figure on the one hand and a minority one on the other, are not comparable. The fact is, that from what we know of the sex-incidence of the disease from post-mortem data, the reverse is more in accordance with the truth, namely, that of all the actual—not merely the discovered—cases of secondary syphilis, men are more liable than women to constitutional upset.

There can be no doubt that the cutaneous reaction in the early syphilis of women is of a much milder character than it is in men.

Syphilis delivers its death-thrust at men through the cardiovascular and nervous systems. Involvement of these is so rare or so trivial in women, that practically it amounts to this, that the disease does not kill members of the female sex.

There is no time, nor indeed do I think there is any

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need, to go into the matter of male and female neurosyphilis in any detail. It will be sufficient if I merely mention the broad facts. The most convenient manifestation to consider is that of general paralysis of the insane. During the five-year period from 1908 to 1912, the comparative incidence of dementia paralytica in England and Wales was 5,352 males and 1,028 females, giving the proportion per 1,000 of the sex-populations of 3.07 males and 0.55 females. If we take the age period of from twenty-five to fifty-four years, the proportions per 1,000 of the respective sex-populations are 7.12 males and 1.23 females.

Viewing these figures in the light of Warthin's⁸ finding, that syphilis is at least as prevalent among women as among men, we cannot but fail to be struck by the extraordinary immunity presented by the female central nervous system to the ravages of the *treponema pallidum*. And what is true of paresis is equally true of tabes.

For the pathological picture we must return to Warthin.⁹ He identifies lesions of the heart and aorta in 100 per cent. of male syphilitics. They are exceedingly rare in women. In that sex they are discovered with difficulty, and, when found, are of very slight degree. The same holds good with respect to syphilitic myocarditis.

Hepatic syphilis is more common among women and particularly among those who have passed the menopause. This hepatitis as a rule escapes clinical recognition.

Gumma of the spleen, splenitis, and perisplenitis, while common in women, are rare in men.

Rectal syphilis—which, like the hypertrophic cervical chancre, is often diagnosed as carcinoma—is much more common in the female sex. The same is true of syphilitic pancreatitis.

Warthin finds syphilis of the suprarenal glands so common in women that he has come to regard it as the most important histological criterion in deciding as to the presence of that disease in the female body which shows no luetic evidence in heart or aorta. This may have some relationship to vitiligo—the syphilitic leucoderma, usually of the neck—which is practically confined to women. Where this vitiligo occurs, the adrenal

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damage is especially well marked. One might regard the leucoderma—or, rather, the surrounding pigmentation—as the localised bronzing of an Addison's disease.

The ovary appears to be immune to syphilis, and this is in very striking contrast to the testis. One of the most constant marks of syphilis in the male is the involvement of the sex-gland.

“Given a man's heart, aorta, and testes, one can tell whether he has had syphilis or not ; but given a woman's heart, aorta, and ovaries, little or no evidence can be gained.”

The ovary is the acme of anabolism, the testis of katabolism. Ovum and spermatozoön are lipoid-rich, but the former is more so than the latter, is more passive, and less highly organised.

We must now try to focus the serological reaction in its relationship to the sex factor—that is to say, to lipoids.

The parasite is a protozoön. It is to be distinguished in many ways from bacteria. The latter are easily culturable. When injected into the body, they produce definitely specific antibodies or amboceptor. These antibodies or antisera can be used prophylactically and therapeutically.

In the case of the protozoa—syphilis, malaria, and so on—we have quite a different story. To make a culture is difficult—perhaps impossible. Antisera cannot be made in the same way as for bacteria. When the parasites are injected into the body we do not get the formation of specific antibodies. Antibody production certainly occurs, but it is not of a specific character for the parasite in question.

Using the terms in their broadest sense, it may be said that protozoa are symbiotic for animals, while bacteria are parasitic for them. And conversely, bacteria are symbiotic for vegetables, while protozoa are parasitic upon them.

In the instance of protozoa and animals—which is that with which we are concerned—the symbiosis is not, of course, absolute, but it is always most pronounced in one type of host. That host to which the parasite does the least harm is said to be the “natural host.” Now, syphilis is confined to one genus—Man—and from what we have seen of its effects upon the respective sexes, we are compelled logically to regard the female as being the

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natural host or carrier of the disease. She it is who lives in the greater harmony with the parasite by virtue of her higher lipid-content. She provides the optimum soil and climate.

It is interesting to note in passing, that since the parasite of syphilis depends upon the human race for its existence, it does not kill its host directly. His death is really accidental, and he dies not so much from the syphilitic attack—not from a toxæmia, as in a bacterial disease—but rather from the secondary effects of the defensive reaction of his own tissues—from fibrosis and its sequelæ. But rarely does this fibrosis in the female reach such a degree that death results—and only then because of a low degree of metabolic femaleness.

Owing to the radical difference between a protozoal and a bacterial disease, it is not to be expected that a specific bacterial complement fixation test should run exactly parallel to a non-specific protozoal one.

The chief characteristic of the physical and chemical constitution of protozoa is that they are rich in lipoids and that they have an affinity for tissues of a like nature. This is especially so in respect of the *treponema pallidum*. It is a lipid-rich attacker of lipid-rich tissues.

When it attacks such tissues, lipo-proteins are formed which are set free into the circulation. These stimulate the production of lipo-proteolytic ferments—antibodies or amboceptors—which become bound to lipid-rich tissue and which exercise a lytic action upon protozoal organisms. They have both a *combinative-tissue* action and a *lytic-organismal* action. These ferments, which are simply antibodies for lipoids, again attack fresh lipid-rich organisms and tissues, more lipo-proteins and ferments are produced, and so the game goes on.

Although the ferments are antibodies, they are not absolutely specific for any particular type of protozoan parasite. They act upon all protozoa and lipid-rich tissue. Their specificity or power increases directly with the lipid-content of the parasite. In like manner, their affinity for body-tissue varies directly with the lipid-richness of that tissue. Furthermore, the higher the lipid-content of the parasite injected, the more severe will be the attack upon lipid tissue and the greater the production of ferment.

In a protozoal complement fixation test such as the

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Wassermann, we are concerned primarily not with the parasites, but with their essential and characteristic lipoids. If then a patient has syphilis—or more accurately, if his syphilis is such that there has occurred a sufficient destruction of lipoid-rich tissue—then his serum will contain an appreciable amount of lipo-proteolytic ferment or amboceptor, and so will give a positive result to the Wassermann test.

In the antigenic system of this test, we have complement composed of guinea-pig serum, amboceptor or patient's serum containing lipo-proteolytic ferment, and antigen consisting of an alcoholic, and perhaps cholesterolinised, extract of heart muscle. This last, it will be noted, is a highly organised lipoid-rich tissue, because we are testing for not a specific bacterial antibody, but for a ferment which has an affinity for such tissue. If there is sufficient of the ferment in the serum to be tested, it will interact or combine with the antigen in the presence of complement—which last will be completely used up in the process. Lysis will thus not occur in the hæmolytic system when that is added—that is, the result of the test will be positive.

Why is it, then, that women who have syphilis, and especially when they are pregnant, so frequently show a negative serology? Either they do not produce sufficient of the ferment to give a positive result, or that, although the production of the antibody is adequate, it does not reach the serum in sufficient quantity to be detected.

We have seen how the serological reaction depends upon the affinity of this antibody-ferment for lipoid tissue. We have also seen that the essential characteristic of femaleness is just exactly this lipoid-richness. It would appear, then, that although antibody or amboceptor is produced both rapidly and adequately in female syphilis—probably more quickly and in greater quantity than in the male—owing to the high lipoid-content of the woman, such antibody is, owing to the same factor, almost immediately anchored to the lipoid-tissues for which it has so avid an affinity. It is thus prevented to a greater degree from reaching the serum in sufficient quantity to be detected by the Wassermann test.

The general rule, then, is that the higher the lipoid-content of the patient, the greater the amount of ferment produced, but the less of it will there be free in the serum.

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So it is that during pregnancy, when the bodily lipid-richness is markedly increased, there is a still greater tendency for the Wassermann to be negative. Pregnancy, lactation and even menstruation may be regarded as conditions of anabolic overflow. In a few moments we shall see how all this checks up with and is related to what we know of malarial therapy.

The amboceptor, which is bound to the tissues, confers upon them a degree of immunity to the parasitic attack. We have here, then, an explanation of why the heart and nervous system in women are specially preserved from syphilitic damage. In addition, it will be noted that, since women by virtue of their high lipid-content produce a superabundance of antibody-ferment, not only are their tissues protected, but there is sufficient ferment to combine with large numbers of parasites and to reduce their virulence considerably.

While we know that for all practical purposes a positive Wassermann test indicates syphilis, yet it is important to recall that the test *does* give a positive result at times in diseases other than syphilis. Examples are: Yaws, the tubercular form of leprosy, some cases of malaria during the paroxysm, diabetes with acidosis, and in generalised carcinomatosis and sarcomatosis. In these diseases we are dealing either with a protozoal infection or with a condition which is equivalent, inasmuch as there is a destruction of lipid-rich tissue with the setting free into the circulation of lipo-proteins and their anti-ferments.

From these metabolical, clinical, pathological, and serological data, I suggest that we have been apt to accept too easily and uncritically the idea that syphilis is much less prevalent among women than among men.

Where the criteria of diagnosis are—as they are bound to be in the living—clinical and serological, the conclusion is not accurate. In reality it implies nothing more than that, with the diagnostic measures applicable to the living—which measures as we have seen so frequently fail to identify the female disease—syphilis is *discovered* less often among women than among men. It does *not* mean that its actual incidence is less in the female sex. The histopathological investigations of Warthin show clearly that there are if anything more female than male carriers of the *treponema pallidum*.

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Let us see where we are now !

We have collected and examined certain facts and observations relative to syphilis in the male and in the female. Reasoning inductively from these, we have arrived at a certain explanation of them—an *hypothesis*. From that hypothesis we have deduced certain other facts and presumptive facts. If the hypothesis be true, then these are all capable of proof. The hypothesis can only be destroyed or be shown to be incomplete if facts predicted by it do not appear, or if others are found for which it cannot account.

Facts and observations are, by themselves, a worthless, inert, and indigestible mass until they are vivified by the vitamins of reasoning and imagination. Deductive and inductive processes must be linked together, controlled, and co-ordinated by imagination—without which last scientific research is impossible. An hypothesis is an essential preliminary to any scientific experiment.

Our facts and observations show that the course of syphilis is considerably modified by the sex of the person affected. I have tried to show that sex is a matter not of morphology but of metabolism, and particularly of lipoids. I have formulated an hypothesis to account for the facts, and I propose now, in conclusion, to indicate at least one practical point, deducible from the hypothesis, which is capable of experimental proof.

What I have been trying to answer is not so much “ *Why is syphilis milder in the female ?* ” but rather “ *Why is it more virulent in the male ?* ” It is, I think, important to appreciate what the difference really is in these two ways of putting the matter. It is, in my view, essential, from the biological, the sociological, and also the practical therapeutic standpoints, to realise that *female syphilis is the normal* and male syphilis the *abnormal* disease. We have tended to look at it the other way round, and that, I am convinced, is wrong.

If we consider the female course of syphilis to be the normal one, if we look upon the woman as the natural host with whom the parasite lives in greater amity, we obtain a very definite clue as to the *modus operandi* of certain chemical and other therapeutic measures as well as an indication of the lines along which further advance must be made. The sex-frontier is a metabolic one. On one side is the katabolic male with a low lipoid-content ;

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on the other is the anabolic female with a high lipid-content.

The practical point capable of experimental proof to which I referred a moment ago, is closely related to the matter of malarial therapy.

In 1924 I did a little work with reference to a sterile milk protein as an adjunct to chemotherapy. It was found that some cases, especially those which were drug-resistant or Wassermann-fast, showed a great clinical and serological improvement. It was also noted that sometimes the milk protein had the provocative effect of converting the serology from negative to positive in uncured cases.

These results were thought to be due, firstly, to protein shock with the stimulation of antibody formation, and, secondly, to pyrotherapy—a rise of temperature being noted in some instances. This latter was considered to be akin to inoculation malaria.

A fresh examination of the question was brought about by Schumacher's¹⁰ and by Hardesty's¹¹ work. It would appear that in malarial therapy, the influence of the fever—the actual rise of temperature—is not so important as has been imagined. The pyro element seems to be incidental and accidental.

We have seen the biochemical similarity between the *treponema pallidum* and, for example, nervous tissue—the lipid-richness. We know, moreover, that not only does the parasite attack such tissues by preference, but that it is much more difficult to eradicate from them than from those which are poor in lipoids. It is also much more difficult to cure syphilis in women than in men—cure, of course, being judged by histological, not clinical and serological, criteria.

Levaditi has shown with respect to bismuth and arsenobenzene, that the tissues which produce the greatest amounts of bismoxyl and arsenoxyl are those which have a high lipid-content. When the relationship between lipoids, syphilis, and remedial agents is considered, it begins to be clear why, for example, a *liposoluble* bismuth salt, such as bivatol, is of so much greater therapeutic value than any other. It also explains why the curative effect of arsenobenzene compounds is greater when given intramuscularly than when given by the intravenous route.

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When discussing complement fixation tests, we saw that there are employed as antigens—that is, as substitutes for dead treponemata—lipoidal extracts of highly specialised organs and tissues such as the heart. Cholesterinised antigens are sometimes used, and we know, of course, that cholesterol is a lipoid.

It has been shown also that when lipoids or proteins are injected alone, the serum remains negative, but that when they are injected together, the reaction may become positive, even in those who have never had syphilis.

When arsenobenzene or bismuth is injected, arsenoxyl or bismoxyl is produced. These *also* have an affinity for tissues rich in lipoids. These substances combine directly, not only with the parasites, thus killing them, but *they also become bound to tissues with a high lipoid-content, especially that of the nervous system.*

In general paralysis of the insane, the parasites are *deeply embedded* in the tissues. The chemical remedial agents reaching the nervous system tend, first of all, to become bound to the tissues. They are thus to a great extent neutralised or absorbed by this “*lipo-protein sponge*” before they can reach the more inaccessible treponemata. This explains the comparative failure of chemotherapy in neurosyphilis.

Upon the induction of malaria, the first effect is a destruction of erythrocytes. The serum is flooded with *dead autogenous* lipo-proteins from the destroyed red corpuscles. These act as stimuli for the production of lipo-proteolytic enzymes, which act not only against treponemata, but also against the malarial parasite itself. And at a later stage, when the fever is terminated by quinine, the plasmodia are all killed off, and again much *dead foreign* lipo-protein is thrown into the circulation. This again stimulates the production of the anti-ferment.

Inoculation malaria, then, causes the production of a large quantity of lipo-proteolytic ferment. In addition to attacking the treponemata which have survived the ordinary chemotherapeutic bombardment, this ferment combines with the lipoid-rich nervous tissues. It thus prevents the arsenoxyl and bismoxyl which will subsequently be administered from becoming bound to these tissues, so making these substances available for attacking the deeply seated organisms.

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What applies to neurosyphilis applies with equal force to visceral syphilis.

If there could, therefore, be introduced into the serum an adequate amount of lipo-proteolytic ferment in the sero-negative and early sero-positive stages of syphilis, then the vital lipoid-rich tissues of the viscera and central nervous system would be protected from attack. In cases of early male syphilis, such a therapeutic procedure ought to make cardiovascular and neurosyphilis as rare and as slight in men as it is in women. Some workers have been using inoculation-malaria in such early cases, but the obvious disadvantages of this prevent its routine use.

The first practical question then comes to be : Can a sufficiency of lipo-proteolytic ferment be introduced by some means other than the induction of a grave febrile disease such as malaria, with its many dangers and objections ? For the present, at any rate, we must return a negative answer.

The second question is : Can a lipo-protein mixture be made artificially which, when injected, will stimulate the production of treponemicidal and combinative anti-ferment and thus secure the end-result of inoculation malaria, which will be applicable to all stages of syphilis, and which can be carried out with the patient in an ambulant condition ? In this case, the answer is in the affirmative.

I suggest that the future therapy of syphilis lies along these lines :—

- (1) The administration of artificially produced arsenoxyl and bismoxyl. This would permit of accurate dosage, complete utilisation of the agents, no strain of manufacture upon the tissues, freedom from toxicity, and shortening the duration of treatment.
- (2) The adjuvant administration of artificially produced lipo-proteolytic ferment.

There are certain practical manufacturing difficulties in the way of both of these at the present moment, but it is only a matter of a little time before they are overcome. When that time arrives, then one may freely indulge in concurrent treatment—it will, in fact, then be indicated—for we should then be supplying the patient with the

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finished article and would not, as at present, be asking him to manufacture it from the raw material provided.

With the chemotherapeutic agents which we at present have (arsenobenzene and bismuth) we may most surely adopt as an adjunct to them the injection of an artificially produced lipo-protein mixture. This will stimulate the production of treponemicidal and combinative ferments of a lipo-proteolytic nature, will protect the viscera and central nervous system, and will enhance the therapeutic value of the chemical remedial agents.

I am engaged upon a work of this kind now, but some time must elapse before an assessment can be made of results. Hardesty's work upon the same lines showed that all the patients did better than with chemotherapy alone; and that in neurosyphilis, the results were equal to those obtained with malarial therapy.

A lipo-protein mixture (L.P.M., for short) is made. The lipoid part is a Wassermann antigen, and milk, for example, forms the protein part. This is given intramuscularly. It remains yet to be seen how best it should be administered—between arsenobenzene and bismuth series, concurrent with one or other, or only before chemotherapy is commenced. I am going a little further than Hardesty did, and am trying to get a better protein than milk, and with that to make a satisfactory mixture of arsenobenzene and L.P.M. and of the bismuth salt of bivitol and L.P.M. Of course, the ideal is to obtain a mixture of arsenoxyl, bismoxyl, and L.P. ferment.

The conclusions I would submit are these :—

- (1) The female is the natural host or carrier of syphilis.
- (2) This is because of her high lipoid-content which is the essential characteristic of femaleness.
- (3) It is because of the low lipoid-content of the male that the disease is in him so severe.
- (4) The abundant production of L.P. ferment by the female in response to the inoculation with syphilis is the reason why her central nervous system and cardiovascular apparatus are so immune to the *treponema pallidum*.
- (5) This ferment being bound to the lipoid-rich tissues is the reason why, although a carrier of the parasite, she may exhibit a negative serology.

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- (6) The endeavour of therapy, then, must be, in every stage of syphilis, to provide the body with sufficient ferment to combine with these vital tissues.
- (7) This can be done by the injection of a lipo-protein mixture.

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